What is Claimed is:

1. A mixture of conjugates each comprising an insulin drug coupled to an oligomer that comprises a polyethylene glycol moiety, wherein the mixture has a dispersity coefficient (DC) greater than 10,000 where

$$DC = \frac{\left(\sum_{i=1}^{n} N_i M_i\right)^2}{\sum_{i=1}^{n} N_i M_i^2 \sum_{i=1}^{n} N_i - \left(\sum_{i=1}^{n} N_i M_i\right)^2}$$

wherein:

n is the number of different molecules in the sample;

N_i is the number of i^{th} molecules in the sample; and

M_i is the mass of the i^{th} molecule.

2. The mixture according to Claim 1, wherein the dispersity coefficient is greater than 100,000.

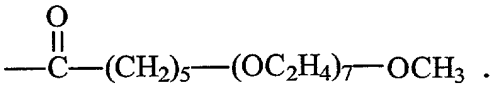
3. The mixture according to Claim 1, wherein the dispersity coefficient is greater than 500,000.

4. The mixture according to Claim 1, wherein the polyethylene glycol moiety has at least 2, 3 or 4 polyethylene glycol subunits.

5. The mixture according to Claim 1, wherein the polyethylene glycol moiety has at least 5 or 6 polyethylene glycol subunits.

6. The mixture according to Claim 1, wherein the polyethylene glycol moiety has at least 7 polyethylene glycol subunits.

7. The mixture according to Claim 1, wherein the insulin drug is human insulin and the oligomer is covalently coupled to Lys^{B29} of the human insulin and has the formula:



8. The mixture according to Claim 1, wherein the mixture has an *in vivo* activity that is greater than the *in vivo* activity of a polydispersed mixture of insulin drug-oligomer conjugates having the same number average molecular weight as the mixture.

9. The mixture according to Claim 1, wherein the mixture has an *in vitro* activity that is greater than the *in vitro* activity of a polydispersed mixture of insulin drug-oligomer conjugates having the same number average molecular weight as the mixture.

10. The mixture according to Claim 1, wherein the mixture has an increased resistance to degradation by chymotrypsin when compared to the resistance to degradation by chymotrypsin of a polydispersed mixture of insulin drug-oligomer conjugates having the same number average molecular weight as the mixture.

11. The mixture according to Claim 1, wherein the mixture has an inter-subject variability that is less than the inter-subject variability of a polydispersed mixture of insulin drug-oligomer conjugates having the same number average molecular weight as the mixture.

12. The mixture according to Claim 1, wherein the insulin drug is insulin.

13. The mixture according to Claim 12, wherein the oligomer is covalently coupled to an amine function of the insulin.

14. The mixture according to Claim 13, wherein the amine function is at Lys^{B29} of the insulin.

15. The mixture according to Claim 12, wherein the conjugate comprises a first oligomer and a second oligomer.

16. The mixture according to Claim 15, wherein the first oligomer is covalently coupled at Lys^{B29} of the insulin and the second oligomer is covalently coupled at N-terminal A1 or N-terminal B1 of the insulin.

17. The mixture according to Claim 1, wherein the insulin drug is covalently coupled to the oligomer.

18. The mixture according to Claim 1, wherein the insulin drug is covalently coupled to the oligomer by a hydrolyzable bond.

19. The mixture according to Claim 1, wherein the insulin is covalently coupled to the polyethylene glycol moiety of the oligomer.

20. The mixture according to Claim 19, wherein the oligomer further comprises a lipophilic moiety covalently coupled to the polyethylene glycol moiety.

21. The mixture according to Claim 1, wherein the oligomer further comprises a lipophilic moiety.

22. The mixture according to Claim 21, wherein the insulin drug is covalently coupled to the lipophilic moiety.

23. The mixture according to Claim 21, wherein the polyethylene glycol moiety is covalently coupled to the lipophilic moiety.

24. The mixture according to Claim 1, wherein the conjugate comprises a first oligomer and a second oligomer.

25. The mixture according to Claim 24, wherein the first and the second oligomers are the same.

26. The mixture according to Claim 1, wherein the oligomer comprises a first polyethylene glycol moiety covalently coupled to the insulin by a non-hydrolyzable bond and a second polyethylene glycol moiety covalently coupled to the first polyethylene glycol moiety by a hydrolyzable bond.

27. The mixture according to Claim 26, wherein the oligomer further comprises a lipophilic moiety covalently coupled to the second polyethylene glycol moiety.

28. The mixture according to Claim 1, wherein the conjugates are each amphiphilically balanced such that each conjugate is aqueously soluble and able to penetrate biological membranes.

29. A pharmaceutical composition comprising:

the mixture according to Claim 1; and

a pharmaceutically acceptable carrier.

30. A method of treating insulin deficiency in a subject in need of such treatment, said method comprising:

administering an effective amount of a mixture of conjugates each comprising an insulin drug coupled to an oligomer comprising a polyethylene glycol moiety, wherein the mixture has a dispersity coefficient (DC) greater than 10,000 where

$$DC = \frac{\left(\sum_{i=1}^{n} N_i M_i\right)^2}{\sum_{i=1}^{n} N_i M_i^2 \sum_{i=1}^{n} N_i - \left(\sum_{i=1}^{n} N_i M_i\right)^2}$$

wherein:

n is the number of different molecules in the sample;

N_i is the number of i^{th} molecules in the sample; and

M_i is the mass of the i^{th} molecule;

to the subject to treat the insulin deficiency.

31. A substantially monodispersed mixture of conjugates, each conjugate comprising an insulin drug coupled to an oligomer that comprises a polyethylene glycol moiety.

32. The mixture according to Claim 31, wherein the polyethylene glycol moiety has at least 2, 3 or 4 polyethylene glycol subunits.

33. The mixture according to Claim 31, wherein the polyethylene glycol moiety has at least 5 or 6 polyethylene glycol subunits.

34. The mixture according to Claim 31, wherein the polyethylene glycol moiety has at least 7 polyethylene glycol subunits.

35. The mixture according to Claim 31, wherein at least about 96, 97, 98 or 99 percent of the conjugates in the mixture have the same molecular weight.

36. The mixture according to Claim 31, wherein the mixture is a monodispersed mixture.

37. The mixture according to Claim 31, wherein the mixture is a substantially purely monodispersed mixture.

38. The mixture according to Claim 31, wherein at least about 96, 97, 98 or 99 percent of the conjugates in the mixture have the same molecular weight and have the same molecular structure.

39. The mixture according to Claim 31, wherein the mixture is a purely monodispersed mixture.

40. A substantially monodispersed mixture of conjugates each comprising human insulin covalently coupled at Lys^{B29} of the human insulin to the carboxylic acid moiety of a carboxylic acid, which is covalently coupled at the end distal to the carboxylic acid moiety to

a methyl terminated polyethylene glycol moiety having at least 7 polyethylene glycol subunits.

41. The substantially monodispersed mixture according to Claim 40, wherein the conjugates each consist of human insulin covalently coupled at Lys^{B29} of the human insulin to the carboxylic acid moiety of hexanoic acid, which is covalently coupled at the end distal to the carboxylic acid moiety to a methyl terminated polyethylene glycol moiety having 7 polyethylene glycol subunits.

42. A substantially monodispersed mixture of conjugates each comprising an insulin drug coupled to an oligomer that comprises a polyethylene glycol moiety, said mixture having an *in vivo* activity that is greater than the *in vivo* activity of a polydispersed mixture of insulin drug-oligomer conjugates having the same number average molecular weight as the substantially monodispersed mixture.

43. The mixture according to Claim 42, further having an *in vitro* activity that is greater than the *in vitro* activity of the polydispersed mixture of insulin drug-oligomer conjugates.

44. The mixture according to Claim 42, further having an increased resistance to degradation by chymotrypsin when compared to the resistance to degradation by chymotrypsin of the polydispersed mixture of insulin drug-oligomer conjugates.

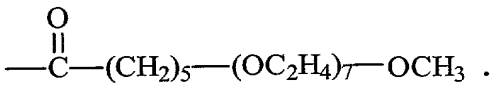
45. The mixture according to Claim 42, further having an inter-subject variability that is less than the inter-subject variability of the polydispersed mixture of insulin drug-oligomer conjugates.

46. A mixture of conjugates each comprising an insulin drug coupled to an oligomer that comprises a polyethylene glycol moiety, said mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons.

47. The mixture according to Claim 46, wherein the standard deviation of the molecular weight distribution is less than about 14 Daltons.

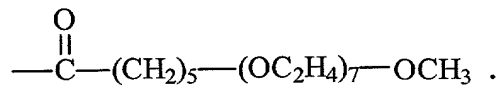
48. The mixture according to Claim 46, wherein the standard deviation of the molecular weight distribution is less than about 11 Daltons.

49. The mixture according to Claim 46, wherein the insulin drug is human insulin and each oligomer is covalently coupled to Lys^{B29} of the human insulin and has the formula:

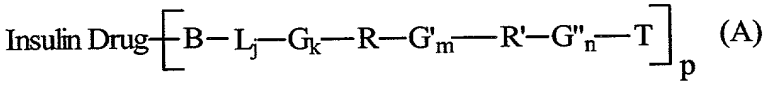


50. A mixture of conjugates in which each conjugate:
comprises an insulin drug coupled to an oligomer; and
has the same number of polyethylene glycol subunits.

51. The mixture according to Claim 50, wherein the insulin drug is human insulin and each oligomer is covalently coupled to Lys^{B29} of the human insulin and has the formula:



52. A mixture of conjugates in which each conjugate is the same and has the formula:



(A)

wherein:

B is a bonding moiety;

L is a linker moiety;

G, G' and G" are individually selected spacer moieties;

R is a lipophilic moiety and R' is a polyalkylene glycol moiety, or R' is the lipophilic moiety and R is the polyalkylene glycol moiety;

T is a terminating moiety;

j, k, m and n are individually 0 or 1; and

p is an integer from 1 to the number of nucleophilic residues on the insulin drug.

53. The mixture according to Claim 52, wherein the polyalkylene glycol group is a polyethylene glycol moiety.

54. The mixture according to Claim 53, wherein the polyethylene glycol moiety has at least 2, 3 or 4 polyethylene glycol subunits.

55. The mixture according to Claim 53, wherein the polyethylene glycol moiety has at least 5 or 6 polyethylene glycol subunits.

56. The mixture according to Claim 53, wherein the polyalkylene glycol moiety is a polyethylene glycol moiety having at least 7 polyethylene glycol subunits.

57. The mixture according to Claim 53, wherein:

R is alkyl or alkylene;

R' is polyethylene glycol having at least 7 polyethylene glycol subunits;

T is alkyl;

j is 1; and

k, m and n are 0.

58. The mixture according to Claim 53, wherein:

B is carbonyl;

R is C_5 alkylene;

R' is polyethylene glycol having 7 polyethylene glycol subunits;

T is methoxy; and

k, m and n are 0.

59. A process for synthesizing a substantially monodispersed mixture of conjugates each conjugate comprising an insulin drug coupled to an oligomer that comprises a polyethylene glycol moiety, said process comprising:

reacting a substantially monodispersed mixture comprising compounds having the structure of Formula I:

$$R^1(OC_2H_4)_m\text{-}O^-X^+ \qquad (I)$$

wherein R^1 is H or a lipophilic moiety; m is from 1 to 25; and X^+ is a positive ion,

with a substantially monodispersed mixture comprising compounds having the structure of Formula II:

$$R^2(OC_2H_4)_n\text{-}OMs \qquad (II)$$

wherein R^2 is H or a lipophilic moiety; and n is from 1 to 25,

under conditions sufficient to provide a substantially monodispersed mixture comprising polymers having the structure of Formula III:

$$R^2(OC_2H_4)_{m+n}\text{-}OR^1 \qquad (III);$$

activating the substantially monodispersed mixture comprising polymers of Formula III to provide a substantially monodispersed mixture of activated polymers capable of reacting with an insulin drug; and

reacting the substantially monodispersed mixture of activated polymers with a substantially monodispersed mixture of insulin drugs under conditions sufficient to provide a substantially monodispersed mixture of conjugates each comprising an insulin drug coupled to an oligomer that comprises a polyethylene glycol moiety with m+n subunits.

60. The process according to Claim 59, wherein R^2 is a fatty acid moiety or an ester of a fatty acid moiety.

61. The process according to Claim 60, wherein the fatty acid moiety or the ester of a fatty acid moiety comprises an alkyl moiety at least 5 carbon atoms in length.

62. The process according to Claim 59, wherein R^1 is a methyl group.

63. The process according to Claim 59, further comprising:

reacting a substantially monodispersed mixture comprising compounds having the structure of Formula V:

$$R^2(OC_2H_4)_n\text{-}OH \qquad (V)$$

with a methanesulfonyl halide under conditions sufficient to provide a substantially monodispersed mixture comprising compounds having the structure of Formula II:

$$R^2(OC_2H_4)_n\text{-}OMs \qquad \text{(II)}.$$

64. The process according to Claim 63, further comprising:

reacting a substantially monodispersed mixture comprising compounds having the structure of Formula VI:

$$R^2\text{-}OMs \qquad \text{(VI)}$$

wherein R^2 is a lipophilic moiety;

with a substantially monodispersed mixture comprising compounds having the structure of Formula VII:

$$R^3(OC_2H_4)_m\text{-}O^-X_2^+ \qquad \text{(VII)}$$

wherein R^3 is benzyl, trityl, or THP; and X_2^+ is a positive ion;

under conditions sufficient to provide a substantially monodispersed mixture comprising compounds having the structure of Formula VIII:

$$R^3(OC_2H_4)_m\text{-}OR^2 \qquad \text{(VIII); and}$$

reacting the substantially monodispersed mixture comprising compounds having the structure of Formula VIII under conditions sufficient to provide a substantially monodispersed mixture comprising compounds having the structure of Formula V:

$$R^2(OC_2H_4)_m\text{-}OH \qquad \text{(V)}.$$

65. The process according to Claim 59, further comprising:

reacting a substantially monodispersed mixture comprising compounds having the structure of Formula IV:

$$R^1(OC_2H_4)_n\text{-}OH \qquad \text{(IV)}$$

under conditions sufficient to provide a substantially monodispersed mixture comprising compounds having the structure of Formula I:

$$R^1(OC_2H_4)_n\text{-}O^-X^+ \qquad \text{(I)}.$$

66. The process according to Claim 59, wherein the activating of the substantially monodispersed mixture comprises reacting the substantially monodispersed mixture of

polymers of Formula III with N-hydroxy succinimide to provide an activated polymer capable of reacting with an insulin drug.

67. The process according to Claim 59, wherein the insulin drug is human insulin, and wherein the reacting of the substantially monodispersed mixture of activated polymers with a substantially monodispersed mixture of insulin comprises:

reacting the substantially monodispersed mixture of activated polymers with Lys^{B29} of the human insulin to provide a substantially monodispersed mixture of monoconjugates each comprising a human insulin coupled to an oligomer that comprises a polyethylene glycol moiety with m+n subunits.